ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms, powder and solvent for solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 50 micrograms contains a sufficient amount of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol) in a powder for solution for injection, and the corresponding amount of solvent, to provide 50 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment

Predictability of sustained virological response: Patients who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (negative predictive value 100 % for combination therapy, 98 % for monotherapy). Virological response is defined as at least a 2-log decrease or absence of detectable HCV-RNA at Week 12. With combination therapy all patients with genotypes 2 or 3 achieved virological response at Week 12 (see also **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of one year).
- **Genotypes 2 or 3**: It is recommeded that patients are treated for at least six months. The decision to extend therapy to one year should be based on other prognostic factors (e.g., age > 40 years, male gender, bridging fibrosis).

PegIntron monotherapy

As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5
89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5

* Must use vial. Minimum delivery for pen is 0.3 ml.
** For patients > 120 kg, use 80 μg/0.5 ml vial

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin – indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50
76-85	60	80	0.4	64
> 85	75	100	0.4	80

*Must use vial. Minimum delivery for pen is 0.3 ml.

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	$< 0.75 \times 10^9$/l	$< 0.5 \times 10^9$/l
Platelets	$< 50 \times 10^9$/l	$< 25 \times 10^9$/l

Dose reduction for patients who use 0.5 μg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 μg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 μg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 μg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (μg)**	**Vial/Pen Strength (μg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (μg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- Existence of or a history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in

fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 3 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 4** to show the pattern of reported effects for all monotherapy groups.

Table 3 Regimens and patient exposure

Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 4 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 5. Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropaenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide. Following marketing, psychosis and hallucinations have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, sarcoidosis or exacerbation of sarcoidosis and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron. Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

Interferon alfa-2b
Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell

metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 100 copies/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 6 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %
Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)

P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load)

HCV Genotype	Rebetol dose (mg/kg)	P 1.5/R	P 0.5/R	I/R
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 2 million copies/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 2 million copies/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (see table 8)

Table 8 Predictability of sustained response by viral response at week 12 and genotype

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 +ribavirin	Genotype 1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 %(28/110)	0 % (0/28)	100 %
	Genotype 2 and 3	Yes 100 % (56/56)	91 %(51/56)	----
		No 0 % (0/56)	0 % (0/0)	100 %

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified (“pegylated”) derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate

to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity

studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:
Disodium phosphate, anhydrous,
Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

Deliverable volume from pen = 0.5 ml. An overfill is also included for proper dispensing from the pen delivery system.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

36 months

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator). Do not freeze.

6.5 Nature and contents of container

The powder and solvent are both contained in a two-chamber cartridge, Type I flint glass, separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 50 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles

and 24 cleansing swabs.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

PegIntron pre-filled pen contains a powder of peginterferon alfa-2b and a solvent for solution at a strength of 50 micrograms for single use. Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 50 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

Remove PegIntron pre-filled pen from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. After administering the dose, discard the PegIntron pre- filled pen and any unused solution contained in it.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/031
EU/1/00/131/032
EU/1/00/131/033
EU/1/00/131/034

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 February 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms, powder and solvent for solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 80 micrograms contains a sufficient amount of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol) in a powder for solution for injection, and the corresponding amount of solvent, to provide 80 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment

Predictability of sustained virological response: Patients who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (negative predictive value 100 % for combination therapy, 98 % for monotherapy). Virological response is defined as at least a 2-log decrease or absence of detectable HCV-RNA at Week 12. With combination therapy all patients with genotypes 2 or 3 achieved virological response at Week 12 (see also **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of one year).
- **Genotypes 2 or 3**: It is recommeded that patients are treated for at least six months. The decision to extend therapy to one year should be based on other prognostic factors (e.g., age > 40 years, male gender, bridging fibrosis).

PegIntron monotherapy

As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5
89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 μg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin – indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50
76-85	60	80	0.4	64
> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	$< 0.75 \times 10^9$/l	$< 0.5 \times 10^9$/l
Platelets	$< 50 \times 10^9$/l	$< 25 \times 10^9$/l

Dose reduction for patients who use 0.5 μg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 μg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 μg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 μg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (μg)**	**Vial/Pen Strength (μg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (μg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- Existence of or a history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in

fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 3 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 4** to show the pattern of reported effects for all monotherapy groups.

Table 3 Regimens and patient exposure

Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 4 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 5. Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropaenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide. Following marketing, psychosis and hallucinations have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, sarcoidosis or exacerbation of sarcoidosis and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron. Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

Interferon alfa-2b
Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell

metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 100 copies/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 6 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %
Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)

P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load)

HCV Genotype	Rebetol dose (mg/kg)	P 1.5/R	P 0.5/R	I/R
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 2 million copies/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 2 million copies/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (see table 8)

Table 8 Predictability of sustained response by viral response at week 12 and genotype

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 +ribavirin	Genotype 1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 %(28/110)	0 % (0/28)	100 %
	Genotype 2 and 3	Yes 100 % (56/56)	91 %(51/56)	----
		No 0 % (0/56)	0 % (0/0)	100 %

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified (“pegylated”) derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate

to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity

studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:
Disodium phosphate, anhydrous,
Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

Deliverable volume from pen = 0.5 ml. An overfill is also included for proper dispensing from the pen delivery system.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

36 months

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator). Do not freeze.

6.5 Nature and contents of container

The powder and solvent are both contained in a two-chamber cartridge, Type I flint glass, separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 80 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles

and 24 cleansing swabs.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

PegIntron pre-filled pen contains a powder of peginterferon alfa-2b and a solvent for solution at a strength of 80 micrograms for single use. Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 80 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

Remove PegIntron pre-filled pen from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. After administering the dose, discard the PegIntron pre- filled pen and any unused solution contained in it.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/035
EU/1/00/131/036
EU/1/00/131/037
EU/1/00/131/038

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 February 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms, powder and solvent for solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 100 micrograms contains a sufficient amount of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol) in a powder for solution for injection, and the corresponding amount of solvent, to provide 100 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment

Predictability of sustained virological response: Patients who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (negative predictive value 100 % for combination therapy, 98 % for monotherapy). Virological response is defined as at least a 2-log decrease or absence of detectable HCV-RNA at Week 12. With combination therapy all patients with genotypes 2 or 3 achieved virological response at Week 12 (see also **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of one year).
- **Genotypes 2 or 3**: It is recommeded that patients are treated for at least six months. The decision to extend therapy to one year should be based on other prognostic factors (e.g., age > 40 years, male gender, bridging fibrosis).

PegIntron monotherapy

As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5
89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 μg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin – indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50
76-85	60	80	0.4	64
> 85	75	100	0.4	80

*Must use vial. Minimum delivery for pen is 0.3 ml.

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	$< 0.75 \times 10^9$/l	$< 0.5 \times 10^9$/l
Platelets	$< 50 \times 10^9$/l	$< 25 \times 10^9$/l

Dose reduction for patients who use 0.5 μg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 μg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 μg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 μg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (μg)**	**Vial/Pen Strength (μg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (μg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- Existence of or a history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in

fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 3 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 4** to show the pattern of reported effects for all monotherapy groups.

Table 3 Regimens and patient exposure

Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 4 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 5. Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropaenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide. Following marketing, psychosis and hallucinations have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, sarcoidosis or exacerbation of sarcoidosis and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron. Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

Interferon alfa-2b
Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell

metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 100 copies/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 6 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %
Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)

P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load)				
HCV Genotype	**Rebetol dose (mg/kg)**	**P 1.5/R**	**P 0.5/R**	**I/R**
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 2 million copies/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 2 million copies/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (see table 8)

Table 8 Predictability of sustained response by viral response at week 12 and genotype				
Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 +ribavirin	Genotype 1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 %(28/110)	0 % (0/28)	100 %
	Genotype 2 and 3	Yes 100 % (56/56)	91 %(51/56)	----
		No 0 % (0/56)	0 % (0/0)	100 %

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified (“pegylated”) derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate

to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity

studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:
Disodium phosphate, anhydrous,
Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

Deliverable volume from pen = 0.5 ml. An overfill is also included for proper dispensing from the pen delivery system.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

36 months

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator). Do not freeze.

6.5 Nature and contents of container

The powder and solvent are both contained in a two-chamber cartridge, Type I flint glass, separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 100 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles

and 24 cleansing swabs.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

PegIntron pre-filled pen contains a powder of peginterferon alfa-2b and a solvent for solution at a strength of 100 micrograms for single use. Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 100 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

Remove PegIntron pre-filled pen from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. After administering the dose, discard the PegIntron pre- filled pen and any unused solution contained in it.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/039
EU/1/00/131/040
EU/1/00/131/041
EU/1/00/131/042

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 February 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms, powder and solvent for solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 120 micrograms contains a sufficient amount of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol) in a powder for solution for injection, and the corresponding amount of solvent, to provide 120 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment

Predictability of sustained virological response: Patients who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (negative predictive value 100 % for combination therapy, 98 % for monotherapy). Virological response is defined as at least a 2-log decrease or absence of detectable HCV-RNA at Week 12. With combination therapy all patients with genotypes 2 or 3 achieved virological response at Week 12 (see also **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of one year).
- **Genotypes 2 or 3**: It is recommeded that patients are treated for at least six months. The decision to extend therapy to one year should be based on other prognostic factors (e.g., age > 40 years, male gender, bridging fibrosis).

PegIntron monotherapy

As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5
89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 μg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin – indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50
76-85	60	80	0.4	64
> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	$< 0.75 \times 10^9$/l	$< 0.5 \times 10^9$/l
Platelets	$< 50 \times 10^9$/l	$< 25 \times 10^9$/l

Dose reduction for patients who use 0.5 μg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 μg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 μg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 μg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (μg)**	**Vial/Pen Strength (μg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (μg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- Existence of or a history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in

fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 3 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 4** to show the pattern of reported effects for all monotherapy groups.

Table 3 Regimens and patient exposure

Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 4 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 5. Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropaenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide. Following marketing, psychosis and hallucinations have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, sarcoidosis or exacerbation of sarcoidosis and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron. Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

Interferon alfa-2b
Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell

metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 100 copies/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 6 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %
Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)

P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load)

HCV Genotype	Rebetol dose (mg/kg)	P 1.5/R	P 0.5/R	I/R
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 2 million copies/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 2 million copies/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (see table 8)

Table 8 Predictability of sustained response by viral response at week 12 and genotype

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 +ribavirin	Genotype 1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 %(28/110)	0 % (0/28)	100 %
	Genotype 2 and 3	Yes 100 % (56/56)	91 %(51/56)	----
		No 0 % (0/56)	0 % (0/0)	100 %

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified (“pegylated”) derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate

to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity

studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:
Disodium phosphate, anhydrous,
Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

Deliverable volume from pen = 0.5 ml. An overfill is also included for proper dispensing from the pen delivery system.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

36 months

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator). Do not freeze.

6.5 Nature and contents of container

The powder and solvent are both contained in a two-chamber cartridge, Type I flint glass, separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 120 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles

and 24 cleansing swabs.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

PegIntron pre-filled pen contains a powder of peginterferon alfa-2b and a solvent for solution at a strength of 120 micrograms for single use. Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 120 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

Remove PegIntron pre-filled pen from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. After administering the dose, discard the PegIntron pre- filled pen and any unused solution contained in it.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/043
EU/1/00/131/044
EU/1/00/131/045
EU/1/00/131/046

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 February 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms, powder and solvent for solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 150 micrograms contains a sufficient amount of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol) in a powder for solution for injection, and the corresponding amount of solvent, to provide 150 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment

Predictability of sustained virological response: Patients who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (negative predictive value 100 % for combination therapy, 98 % for monotherapy). Virological response is defined as at least a 2-log decrease or absence of detectable HCV-RNA at Week 12. With combination therapy all patients with genotypes 2 or 3 achieved virological response at Week 12 (see also **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of one year).
- **Genotypes 2 or 3**: It is recommeded that patients are treated for at least six months. The decision to extend therapy to one year should be based on other prognostic factors (e.g., age > 40 years, male gender, bridging fibrosis).

PegIntron monotherapy

As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5
89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 μg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin – indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50
76-85	60	80	0.4	64
> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	$< 0.75 \times 10^9$/l	$< 0.5 \times 10^9$/l
Platelets	$< 50 \times 10^9$/l	$< 25 \times 10^9$/l

Dose reduction for patients who use 0.5 μg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 μg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 μg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 μg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (μg)**	**Vial/Pen Strength (μg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (μg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- Existence of or a history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in

fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 3 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 4** to show the pattern of reported effects for all monotherapy groups.

Table 3 Regimens and patient exposure

Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 4 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 5. Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropaenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide. Following marketing, psychosis and hallucinations have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, sarcoidosis or exacerbation of sarcoidosis and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron. Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

Interferon alfa-2b
Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell

metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 100 copies/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 6 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %
Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)

P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load)				
HCV Genotype	**Rebetol dose (mg/kg)**	**P 1.5/R**	**P 0.5/R**	**I/R**
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 2 million copies/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 2 million copies/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (see table 8)

Table 8 Predictability of sustained response by viral response at week 12 and genotype				
Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 +ribavirin	Genotype 1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 %(28/110)	0 % (0/28)	100 %
	Genotype 2 and 3	Yes 100 % (56/56)	91 %(51/56)	----
		No 0 % (0/56)	0 % (0/0)	100 %

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified (“pegylated”) derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate

to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity

studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:
Disodium phosphate, anhydrous,
Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

Deliverable volume from pen = 0.5 ml. An overfill is also included for proper dispensing from the pen delivery system.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

36 months

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator). Do not freeze.

6.5 Nature and contents of container

The powder and solvent are both contained in a two-chamber cartridge, Type I flint glass, separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 150 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles

and 24 cleansing swabs.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

PegIntron pre-filled pen contains a powder of peginterferon alfa-2b and a solvent for solution at a strength of 150 micrograms for single use. Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 150 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

Remove PegIntron pre-filled pen from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. After administering the dose, discard the PegIntron pre- filled pen and any unused solution contained in it.

7. MARKETING AUTHORISATION HOLDER

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B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

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